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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,798	08/25/2003	Anurag Rathore.	161765.00520	3621

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HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 8910
RESTON, VA 20195

EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	**PAPER NUMBER**
1654	

MAIL DATE	DELIVERY MODE
06/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,798	RATHORE ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 39-76* is/are pending in the application.

4a) Of the above claim(s) *69-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 39-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, see pages 2-3, filed 5/7/07, with respect to 35 USC 103 rejection of claims 1-34 and 39-68 have been fully considered and are persuasive. The 103 rejection of claims 1-34 and 39-68 has been withdrawn. Applicant's argument that the peptide shown in the figure 1 (page 313) of the cited reference of Andersen, et al., corresponds to SEQ ID NO: 1 of the instant application is correct and hence the rejection of claims under 35 USC 103 of claims 1-34 and 39-68 is withdrawn.

The prosecution of this application has been opened for further consideration.

Claims 1-34 and 39-76 are pending.

Claims 69-76 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 35-38 are canceled.

Claims 1-34 and 39-68 have been examined on the merit.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-68 are rejected under 35 U.S.C. 1.03(a) as being unpatentable over US patent 5,849,535 issued to Cunningham, in view of Jespersen, et al., Eur. J. Biochem., 1994, 219, 365-373, and further in view of Houk, et al., J. Am Chem. Soc., 1987, 109, 6825-6836.

In the instant application, applicants claim a process for decreasing trisulfide impurity in recombinant production of a growth hormone antagonist polypeptide B-2036 (SEQ ID NO: 1) in genetically modified host cells. The steps involved in reducing the trisulfide impurity during the process involved contacting the impurity with a mercapto compound, growing the host cells to produce the polypeptide, purifying the polypeptide and pegylating the polypeptide

Cunningham, et al., discloses a method for the preparation human growth hormone antagonist, B-2036 variants (example V in columns 56-61), that encompass the pegylation of the growth hormone (column 64). The described method meets the limitations of the 10-50 mM tris buffer temperature, pH (column 59), and volume of the buffer used during the process (column 58). The reference the GH variant 2036 was constructed rendering the variant better a better candidate for modification with PEG while **preserving enhanced affinity of the variant for its receptors** (column 55, lines 39-48). The 2036 variant has the following substitutions:

H18D, H21N, G120K, R167N, K168A, D171S, K172R,
E174S, I179T.

It should be noted that the receptor binding activity shows an enhancement and the Cysteine residues at positions 182 and 189 have not been substituted. Therefore the tertiary structure of the variant protein 2036 is comparable to the unmodified GH. However, the method described does not use mercapto compounds as reducing agents to decrease the trisulfide impurity in the preparation.

Jespersen, et al., teaches the characterization of a trisulfide derivative of human growth hormone produced in E. Coli. The reference uses 1,4-dithiothreitol to reduce the full-length derivative of the growth hormone for electrospray mass spectroscopy (page 367, column 1). The reference teaches that the growth hormone has been characterized with a Cys182-Cys189 trisulfide bridge (abstract). Jespersen, et al., also discuss the aspect of trisulfide formation in the E. Coli cells due to the presence of high concentration of H_2S present during Cell disruption (Page 372, column 1). The trisulfide bond could be formed by a HS- attack on a disulfide linkage of the cysteine. The mechanism is reversible and hence the liberation of H_2S was observed with the treatment of cysteine on the growth hormone (page 372, column 2).

The reference of Houk, et al., discusses the structure-reactivity relations for number of thiol compounds, which are functional equivalents of the compounds recited the instant application. The list of compounds (on pages 6830 and 6831) can be used individually or in combinations of others for the purpose of reducing the disulfide bonds or trisulfide linkages.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop a process for decreasing the amount of trisulfide impurity in B-2036 variant of the GH by modifying the teachings of Cunningham to incorporate the teachings of Jespersen, et al. Because, Cunningham had shown that the GH variant B-2036 can be purified from

bacterial culture and Jespersen had shown that the trisulfide derivatives of GH can be characterized by reduction with 1,4-dithiothreitol. The skilled artisan would have been motivated to do so because, the Jespersen had showed that the trisulfide derivatives of GH can be reduced using 1,4-dithiothreitol and the B-2036 although modified with various substitutions at aforementioned sites in the protein still possessed enhanced activity and the Cysteine residues responsible for the trisulfide formation was intact without any modifications in the GH variant B-2036. There would have been a reasonable expectation of success to use mercapto compound for the process of reducing the trisulfide impurity in the recombinant production of B-2036 variant of the growth hormone given the fact that Jespersen, et al., had shown that use of reducing agents such as 1,4-dithiotreitol would reduce the trisulfide bridge in GH and the fact that the B-2036 despite several substitutions at various sites retained activity indicating that the tertiary structure of the protein is similar to the unmodified GH and Hauk, et al., had discussed structure-activity relationships of number of reducing agents which are functional equivalents of the compound claimed in the instant invention.

Therefore, the invention as whole would have been prima facie obvious to one skilled in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande
AU 1654

6/25/07
ANISH GUPTA
PRIMARY EXAMINER